Primary HPV Screening:

Is it coming? Is that OK? Should we do it? Do we have a choice? Does it matter? What next?

49th Annual Vail Ob/Gyn Course

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Vail, Colorado

No COI

- Probably
- Yes
- Yes
- Maybe not
- Probably not
- Something else or at least more changes sooner than later

Learning objectives:

- Review current guidelines for Cx CA screening
- Explain HPV as primary screening method
- Appreciate benefits and limitations of primary screening
- Apply HPV as primary screening

REMEMBER

- These are guidelines and meant to suggest a pathway for evaluation and management
- The recommendations are for screening populations without risks. This does not include Immune-compromised individuals, DES exposure nor follow-up to high grade dysplasia or cancer, or pts without a cervix
- Not so comprehensive as to apply to all clinical situations. Not a substitute for clinical judgment
- Individualized approach should be considered and include shared decision making with the patient to determine best strategy

Cervical Cancer Rates

Global

604,000 (470,600) **cases per year**

342,000 *(233,400)* **deaths per year**

Rates > 40/100,000 women (similar to Anal CA in MSM in US)

4th most common Ca in women and 3rd cause of Ca death

United States

13,800 *(13,000)* **cases per year**

(Oropharyngeal most common HPV-linked cancer)

4290 *(4,100)* **deaths per year- 65% higher in black women**

Rates <5/100,000 women

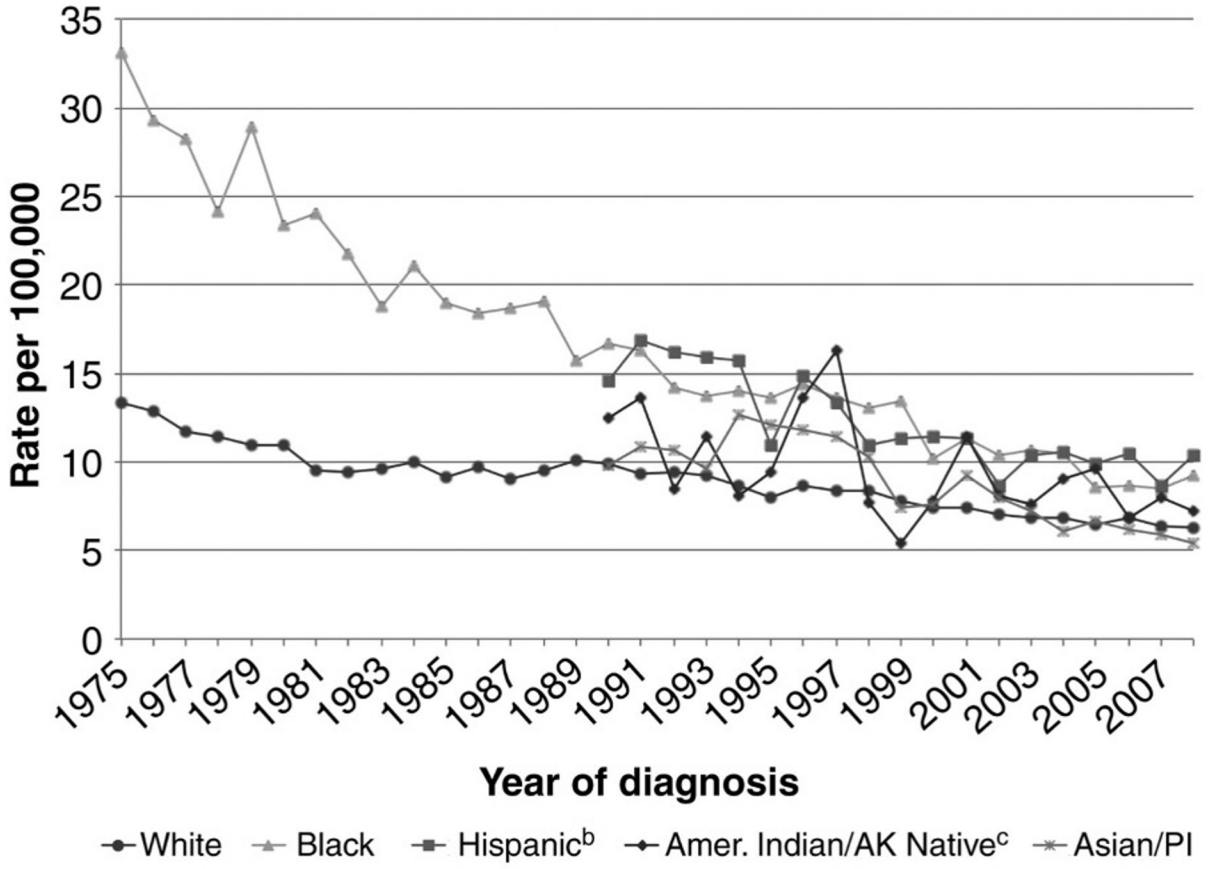
Ranks 18th cancer in women

100,000 Tx'd for Precancer

WHO Health Topics cervical Cancer Nov 2023
Fontham et al. CA: Cancer J Clin. 70,5 2020

Screening Prevents Cervical Cancer

Since screening has been introduced in the United States, the rate of cervical cancer has decreased by 80%.



Pierce Campbell CM, et al. Prevention of invasive cervical cancer in the United States: Past, present, and future. *Cancer Epidemiology, Biomarkers & Prevention*. 2012;21(9):1402–8.

Peto J, et al. The cervical cancer epidemic that screening has prevented in the UK. *Lancet*. 2004;364(9430):249-56.

Management Guidelines: *We've come a long way…. or have we?*

- **1980s Class system: I II III IV and V**
- **1990s Bethesda System: 3 revisions, ASC-US thank you much**
- **2000 Liquid Based Cytology**
- **2003 ALTS data released**
- **2006 ASCCP incorporates HPV management**
- **2011 ASCCP/ACS/ASCP & USPSTF guidelines**
- **2014 FDA approval HPV for primary screening**
- **2015 ASCCP/SGO Interim Guidance for HPV**
- **2016 ACOG endorsed SGO guidelines**
- **2018 USPSTF includes Primary HPV screening**
- **2020 ASCCP "risk based" guidelines**

Additional changes

- Start pap screen w/ sexual debut, 3 yrs after, 18, 20, 21.
- Stop screening 65 or Hysterectomy and no Hx HSIL in low risk population with appropriate screening
- Extended screening intervals 2, 3 and 5 yrs

- Now recommend Primary HPV screening
  - Not HPV only
  - “Reflex Cytology and genotyping”

Traditional fixed cytology slide vs. Liquid Based Cytology

- Historically “old fashioned pap smear” performed well, decreased Cx Ca rates and morbidity 80%
- New liquid-based technology improved screening performance
  - Sensitivity
  - Unsatisfactory/obscured result
  - Readability and efficiency
- In hindsight conventional pap not as sensitive as proposed
- Improved performance with frequent screening
- Splitting hairs? ***Something > Nothing, Any Screen > No Screen***

Risks for Cx CA?

- Early sexual activity, exposure to HPV
- Multiple partners
- HPV infected partners
- No condoms
- Immune compromised
- Lack of vaccine
- Smoking

- Length of time since last pap
- No pap Hx

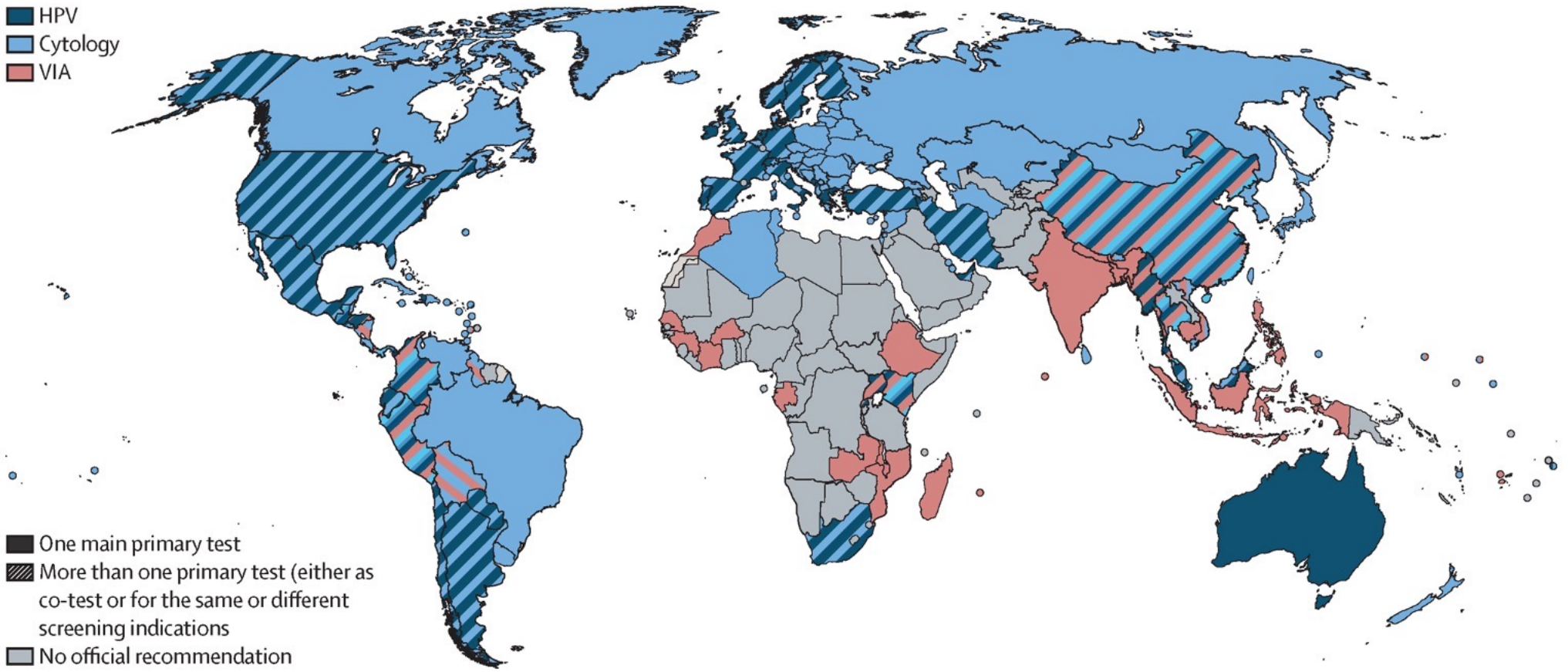
Who recommends Primary HPV Screening?

- **ACS 2020 Outright recommendation Primary HPV Screening Preferred**
- Support/Endorse
  - ASCCP "Supports ACS guidelines. Recognizes the need to transition to Primary HPV Screening"
  - ACOG "ACOG, ASCCP, SGO advise Primary HPV screen may start 25 but initiate Cx CA screen at 21"
  - SGO
  - USPSTF
  - AAFP
  - WHO
  - FIGO
  - ASCO

ASCCP Cx CA Screening Task Force. Jrnl Low Gen Tract Dis. 25,3,July 2021
ACOG.org Cervical cancer Screening Guidelines April 2021

Countries that Recommend Primary HPV Screening

48/139 countries (35%) recommend primary HPV screening as of August 2022



Bruni L, et al. Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. *Lancet Global Health*. 2022;10(8):E1115-E1127.

Cervical cancer screening recommendations from United States professional organizations*[1-6]

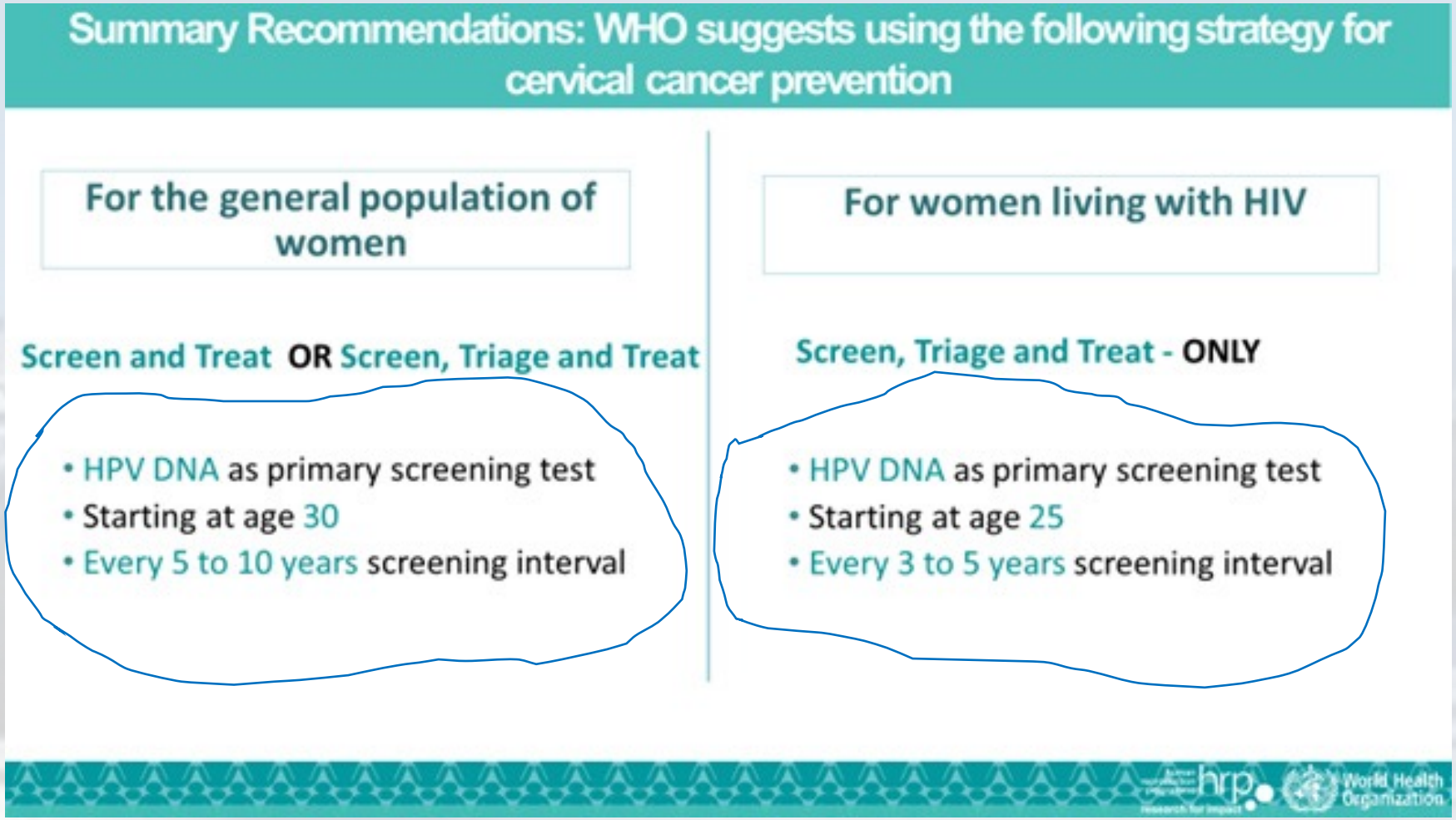
Organization	Age to initiate (years)¶	Age to discontinue (years)	Recommended screening test and frequency		Post-hysterectomy	HPV vaccination
In our practice, we use the following guidelines, in order of preference:						
USPSTF (2018)	21	65Δ	**Age 21 to 29 years** Pap test every 3 years	**Age ≥30 years** One of these methods: •Pap test every 3 years •Primary HPV testing◊ alone every 5 years •Co-testing (Pap test and HPV testing) every 5 years	Not indicated§	Same recommendations as unvaccinated patients
ACS (2020)	25	65¥	**Age ≥25 years** One of these methods: •Primary HPV testing◊ every 5 years (preferred) •Co-testing (Pap test and HPV testing) every 5 years •Pap test every 3 years		Not indicated‡	Same recommendations as unvaccinated patients
ACOG (2021)	21	65Δ	**21-29** pap test every 3 years	**≥30** One of these methods: •Pap test every 3 years •Primary HPV testing◊ alone every 5 years •Co-testing (Pap test and HPV testing) every 5 years	Not indicated§	Same recommendations as unvaccinated patients
ACP (2015)	21	65Δ	Pap test every 3 years	One of these methods: •Pap test every 3 years •Alternative: Co-testing (Pap test and HPV testing) every 5 years	Not indicated§	N/A
ASCCP/SGO (2015 interim guidelines)	21	N/A	Can consider primary HPV testing◊ every 3 years for patients age ≥25	Can consider primary HPV testing◊ every 3 years	N/A	N/A
ACS/ASCCP/ASCP (2012)	21¶	65†	Pap test every 3 years (preferred)	One of these methods: •Co-testing (Pap test and HPV testing) every 5 years (preferred) •Pap test every 3 years	Not indicated**	Same recommendations as unvaccinated patients

Curry SJ. Screening for cervical cancer: United States Preventive Services Task Force recommendation statement. JAMA 2018; 320:674.
Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin 2020.
Updated Cervical Cancer Screening Guidelines. The American College of Obstetricians and Gynecologists. Available at: www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines (Accessed on February 16, 2023).
Sawaya GF, Kulasingam S, Denberg TD, et al. Cervical Cancer Screening in Average-Risk Women: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015; 162:851.
Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. Gynecol Oncol 2015; 136:178.
Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 2012; 62:147.

2020 ACS Recommendations

	2020 ACS	2012 ACS	2018 USPSTF
Age 21–24	No screening	Pap test every 3 years	Pap test every 3 years
Age 25–29	HPV test every 5 years (preferred) HPV/Pap cotest every 5 years (acceptable) Pap test every 3 years (acceptable)	Pap test every 3 years	Pap test every 3 years
Age 30–65	HPV test every 5 years (preferred) HPV/Pap cotest every 5 years (acceptable) Pap test every 3 years (acceptable)	HPV/Pap cotest every 3 years (preferred) Pap test every 3 years (acceptable)	Pap test every 3 years, HPV test every 5 years, or HPV/Pap cotest every 5 years
Age 65 and older	No screening if a series of prior tests were normal	No screening if a series of prior tests were normal	No screening if a series of prior tests were normal and not at high risk for cervical cancer

WHO


Summary Recommendations: WHO suggests using the following strategy for cervical cancer prevention
For the general population of women
Screen and Treat OR Screen, Triage and Treat
• HPV DNA as primary screening test
• Starting at age 30
• Every 5 to 10 years screening interval
For women living with HIV
Screen, Triage and Treat - ONLY
• HPV DNA as primary screening test
• Starting at age 25
• Every 3 to 5 years screening interval
hrp
World Health Organization

Why Primary HPV Screen? *Advantages*

- HPV screening better sensitivity for CIN and CA compared to Cytology
- Objective, less labor, efficient throughput, reproducible
- Comparable sensitivity to Cotesting for detecting CIN and no difference for CA
- More efficient, fewer tests to detect same pathology, fewer exams
- Better detection glandular lesions
- Cost efficient (in the long run)

- Potential for self collection
- Potential improve access and reduce disparities
- Simpler algorithm

Einstein et al. ObGyn.142,5 Nov 2023.
Fontham et al. CA: Cancer J Clin. 70,5 2020

Why Not Cytology Alone? *Pros and cons*

- Cons
  - Costly, labor intensive and subjective
  - Requires skilled cytopathologists, shrinking pool
  - Decreased sensitivity requires increased frequency
- Pros
  - Better specificity than HPV
  - Additional infections- Yeast, trich, BV
  - Endometrial cells
  - Tadpoles
  - Confirm specimen adequacy. What if scant cellularity- trust negative HPV?

Einstein et al. ObGyn.142,5 Nov 2023.
Fontham et al. CA: Cancer J Clin. 70,5 2020

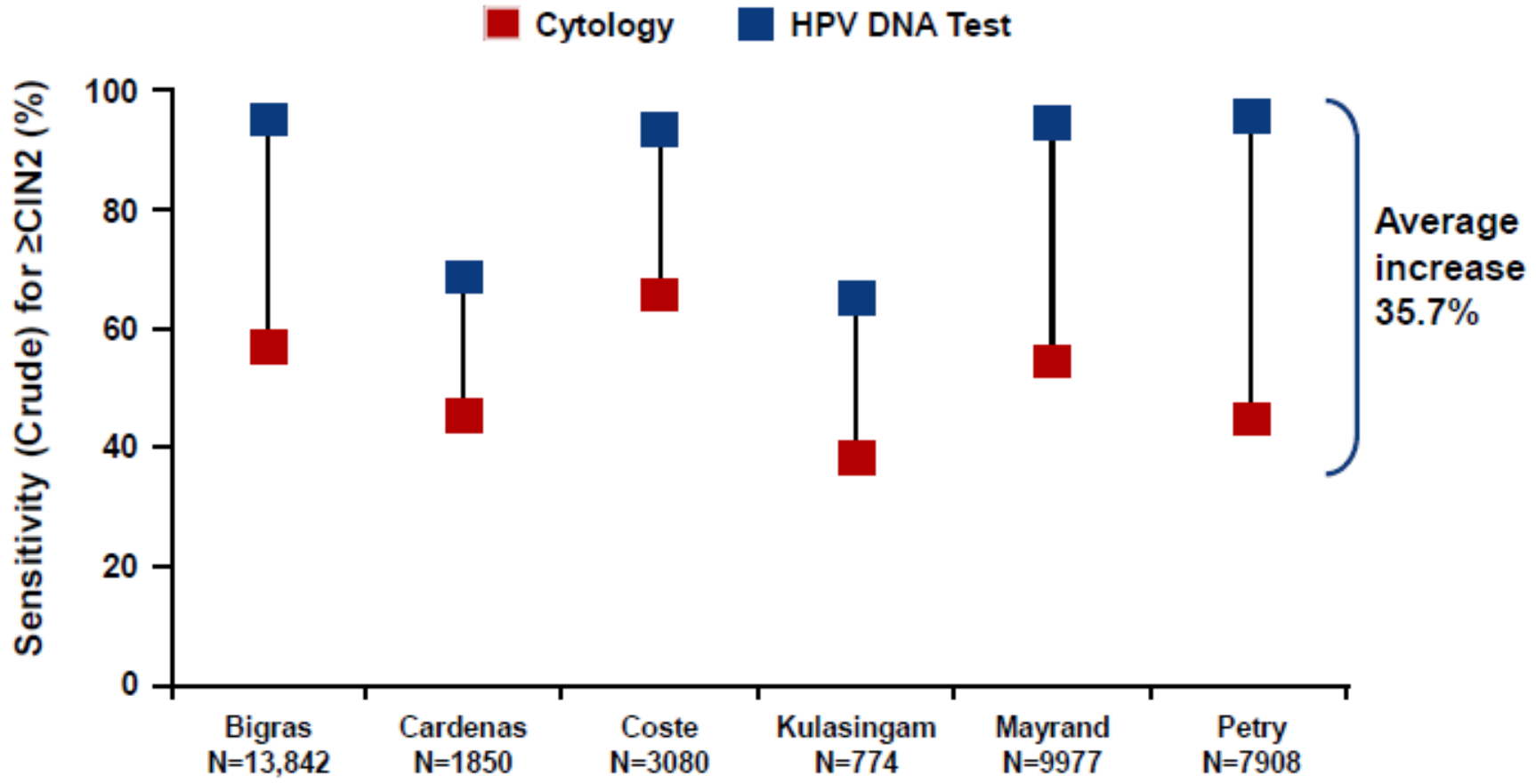
What About CoTesting? *Pros and cons*

- Pros
  - Improves specificity of HPV screen
  - Increase sensitivity of HPV screen (Any additional screening test increases sensitivity), by how much?
  - Detect Non-HPV tumors?
  - Provider and pt acceptability

- Cons
  - Increase test #
  - Increase costs

Einstein et al. ObGyn.142,5 Nov 2023.
Fontham et al. CA: Cancer J Clin. 70,5 2020

Sensitivity of Cytology vs. HPV to Detect HSIL Incident Disease



HPV testing used an HPV assay other than cobas® HPV Test
Studies performed in developed countries in women 30 years and older
Whitlock EP, et al. *Ann Intern Med.*2011; 155:687–697, W214–5.

Far Fewer Cases of CIN3+ over 6 Years in Women Screened with HPV-based Tests than Cytology

Cytology vs. HPV to Detect Future HSIL Disease

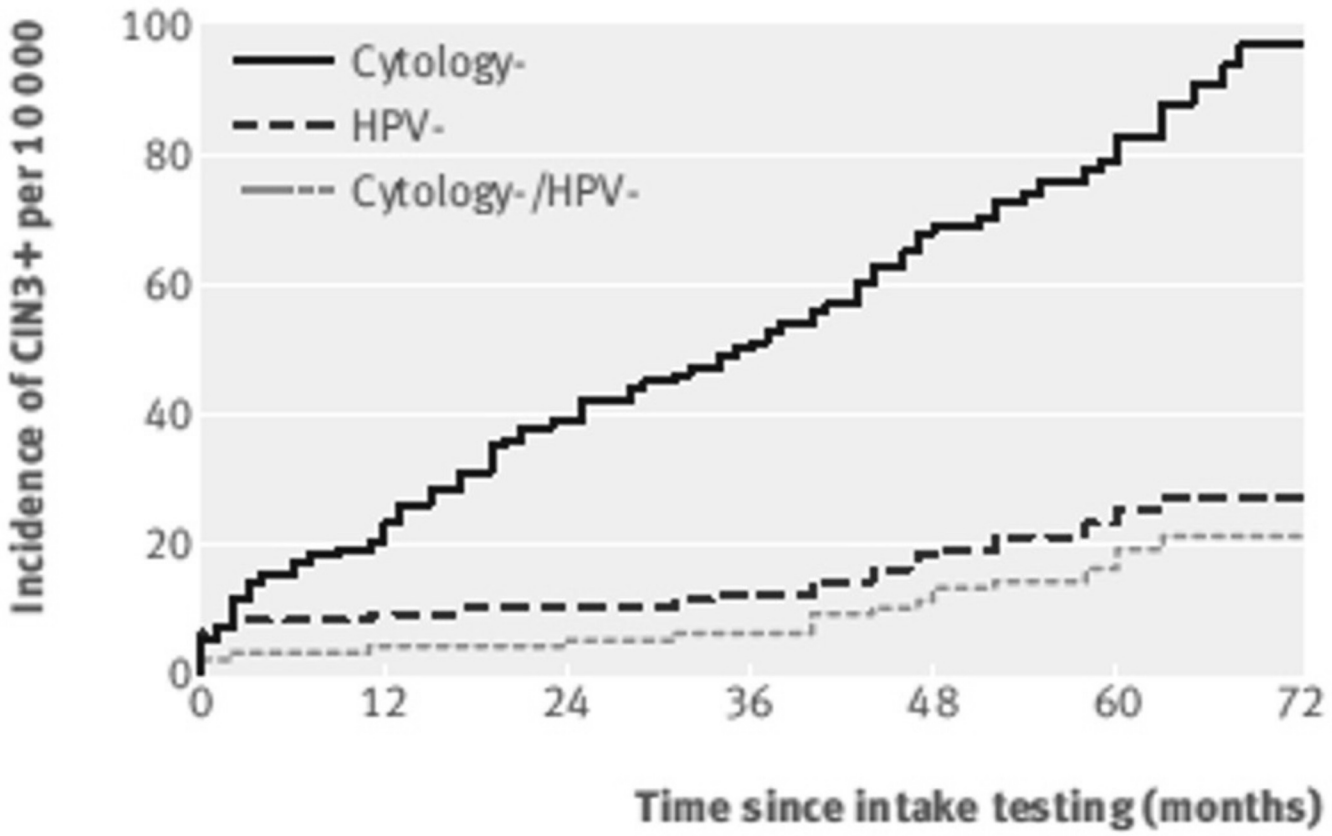


Fig 2 | Kaplan-Meier plots of cumulative incidence rate for CIN3+ for women according to baseline test results in first 72 months of follow-up, excluding Denmark and Tübingen

Dillner J, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: Joint European cohort study. *BMJ.* 2008;337:a1754.

Primary HPV Screening Compared to Cotesting

Primary HPV screening results in similar reduction in cancer rates compared to cotesting, with far fewer tests.

Strategy	Total Tests	Colpos	CIN 2,3	Cancer Cases	Cancer Deaths
No screening	0	0	0	18.86	8.34
Cyto q 3 y age 25-65	13,313	564	142	2.60	0.86
Cyto q 3 y from age 21 then Co-test q 5 y age 30-65	19,806	1,630	201	1.08	0.30
HPV q5 y age 25-65	10,954	1,775	195	0.94	0.28

*Per 1,000 persons with a cervix, screened over a lifetime

Fontham ETH, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020;70(5):321-346.

Primary HPV Screening is the Most Cost-Effective Approach

Screening Modality	Cases of CIN3+ Detected	Number of Colposcopies	Cost
Primary HPV Screening	294	2422	$3.47 M
Primary Cytology	285	2966	$4.80 M
Cotesting	308	2988	$5.85 M

Modeling study based on 99,549 patients with cotesting followed over 3 years.

Jin XW, et al. Cost-effectiveness of primary HPV testing, cytology and co-testing as cervical cancer screening for women above age 30 years. *J Gen Intern Med.* 2016;31(ii):1338-1344.

Limitations for Primary HPV Screening

- Decreased specificity
- Change in workflow, Implementation challenges, initial costs
- Requires specific laboratory testing, 3 FDA approved platforms
  - Roche Cobas®
  - BD Onclarity ™
  - Abbott Alinity m
- Liquid based, Workflow depends on lab, Clinicians coordinate with labs
- Coding and EMR adaptation
- Patient Provider satisfaction

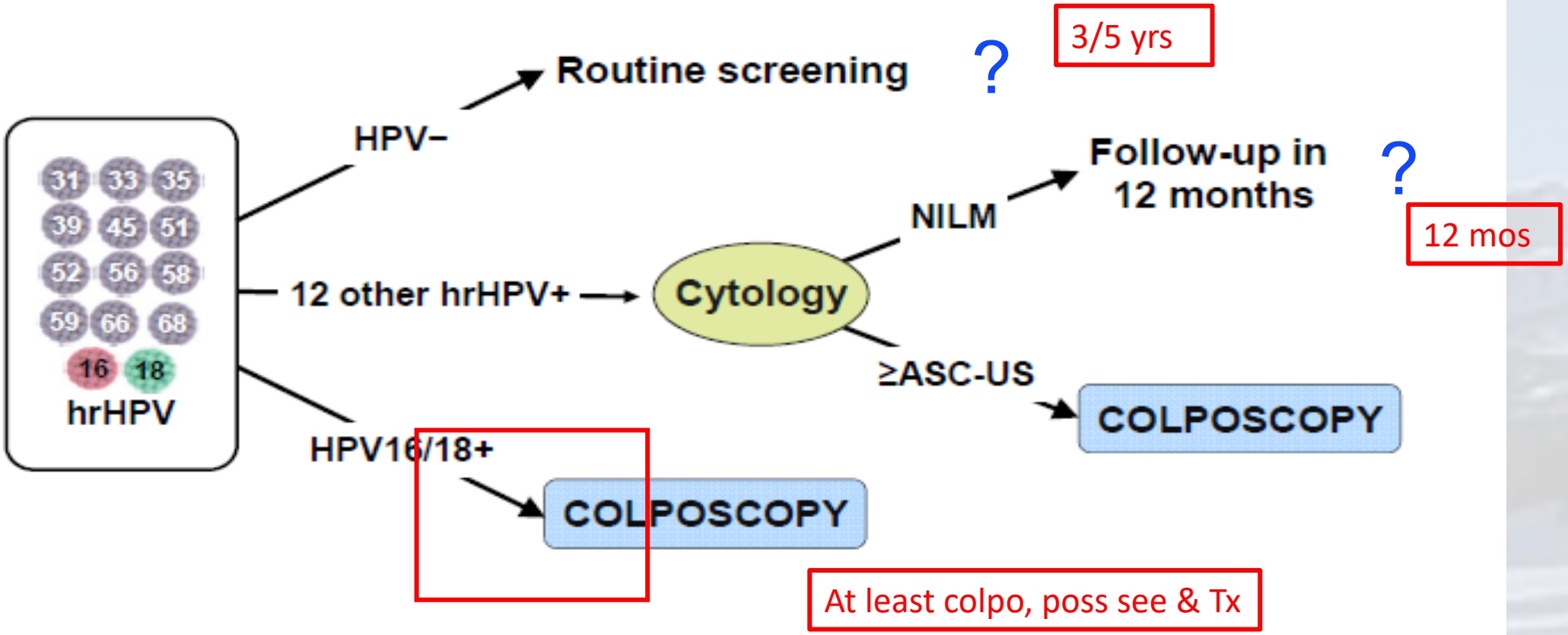
Primary HPV

- Very good test to eliminate pts from close surveillance
- good test for screening pts to identify those at risk of significant dysplasia or cancer

- Not so good at specifically identifying pts needing treatment

- Need additional testing to decide who needs further evaluation and management

Primary HPV Screening – Candidate
HPV with 16/18 Genotyping and Reflex Cytology



hrHPV=high risk HPV

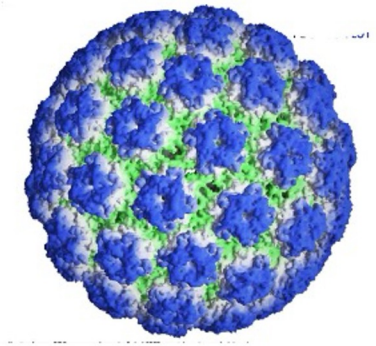
Huh et al. GynOnc. 136, 2015

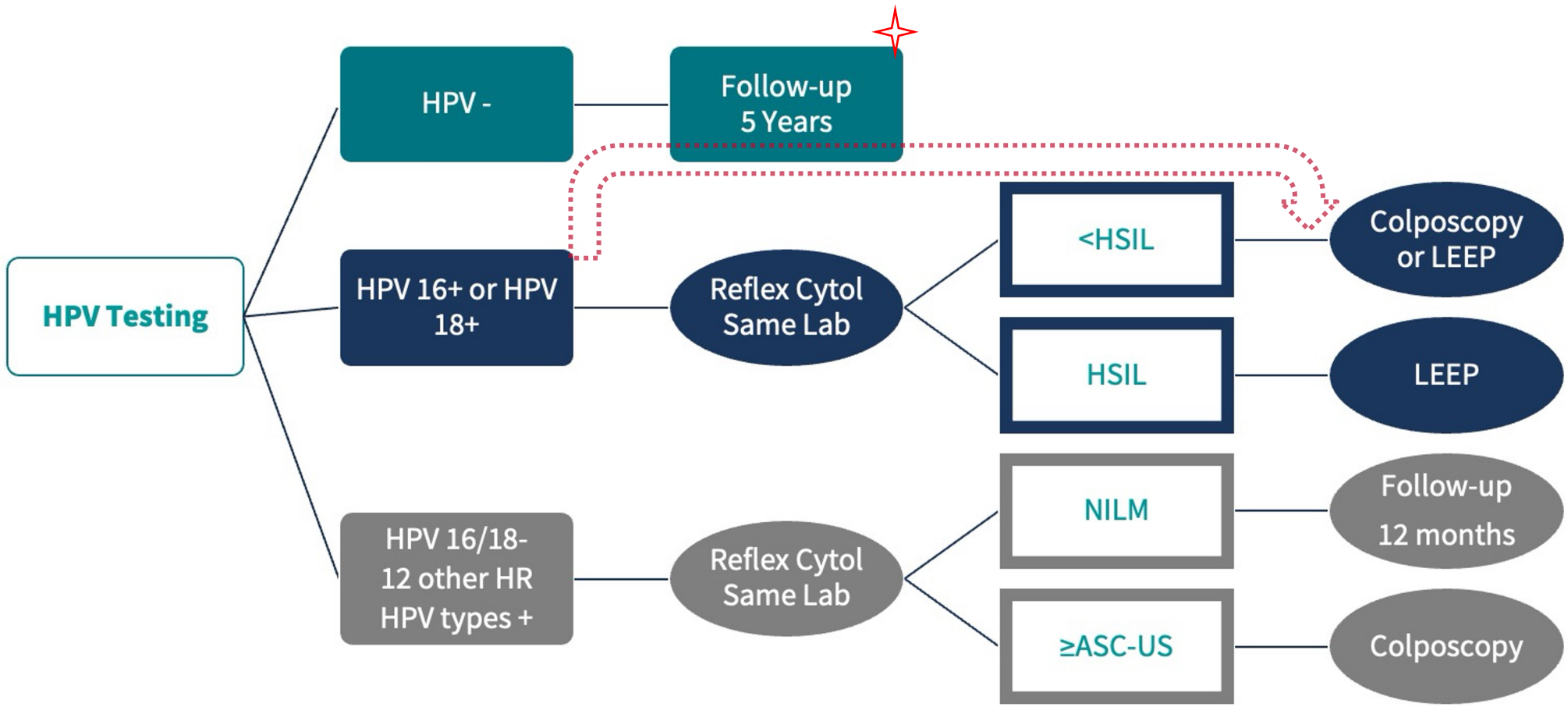
HPV as Primary Screening: SGO/ASCCP Interim Guidelines

- **Initiate at 25**
- **With negative results rescreen no sooner than 3 yrs**
- **Stop at 65 if appropriately screened and negative**
- **Roche COBAS® only system approved originally- now BD and Abbott**
- **Not for use in women s/p hysterectomy**
- **No guidance for immunocompromised or HIV+**
- **How screen HPV+ (Other/Intermediate) but negative 16/18 w/ normal cytology in 12 mos? CoTest reasonable**

Huh et al. GynOnc. 136, 2015

Algorithm for Primary HPV Screening





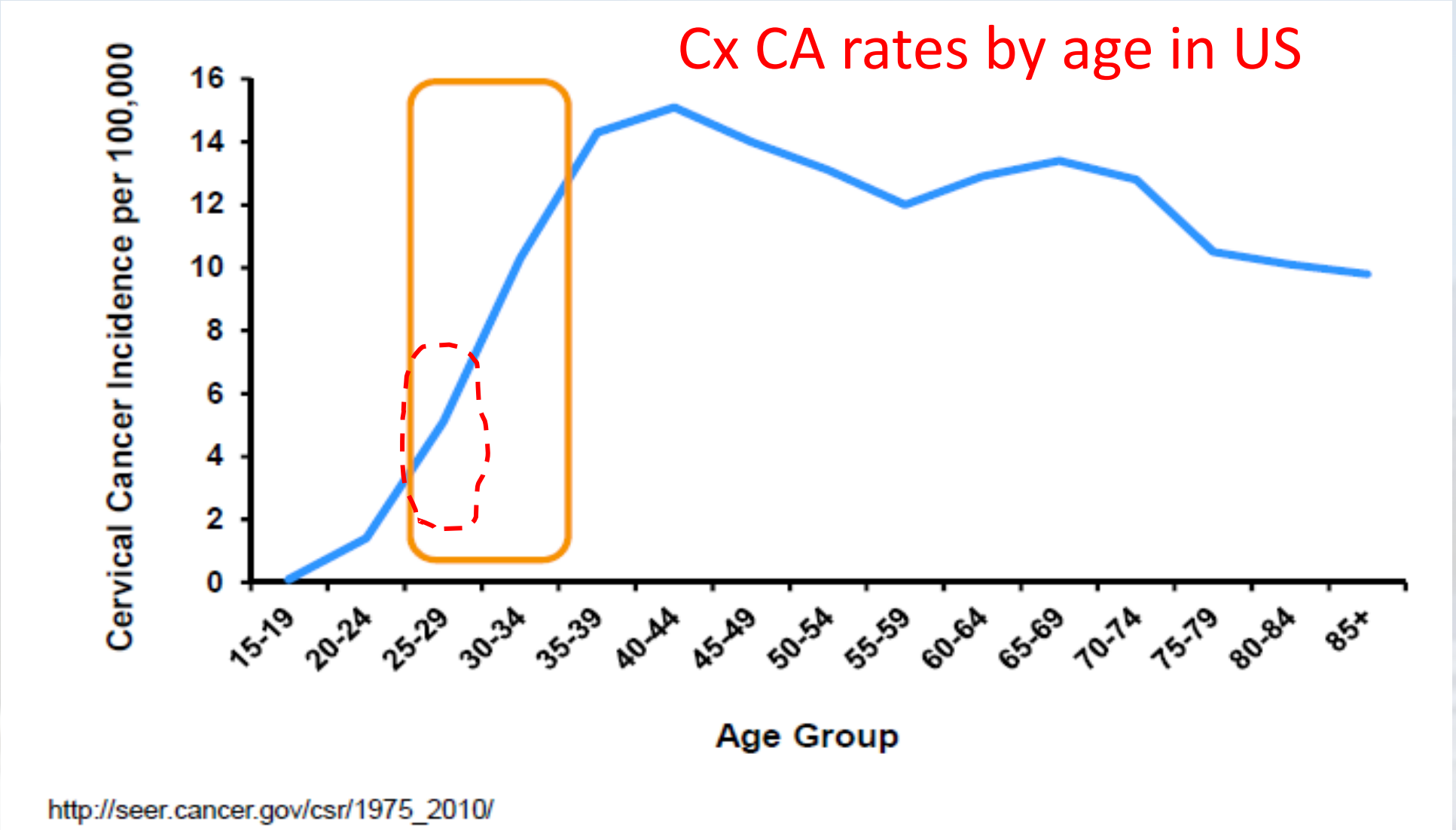
Huh WK, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. *Obstet Gynecol*. 2015;125(2):330-337.

Perkins RB, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Low Genit Tract Dis*. 2020;24(2):102-131.

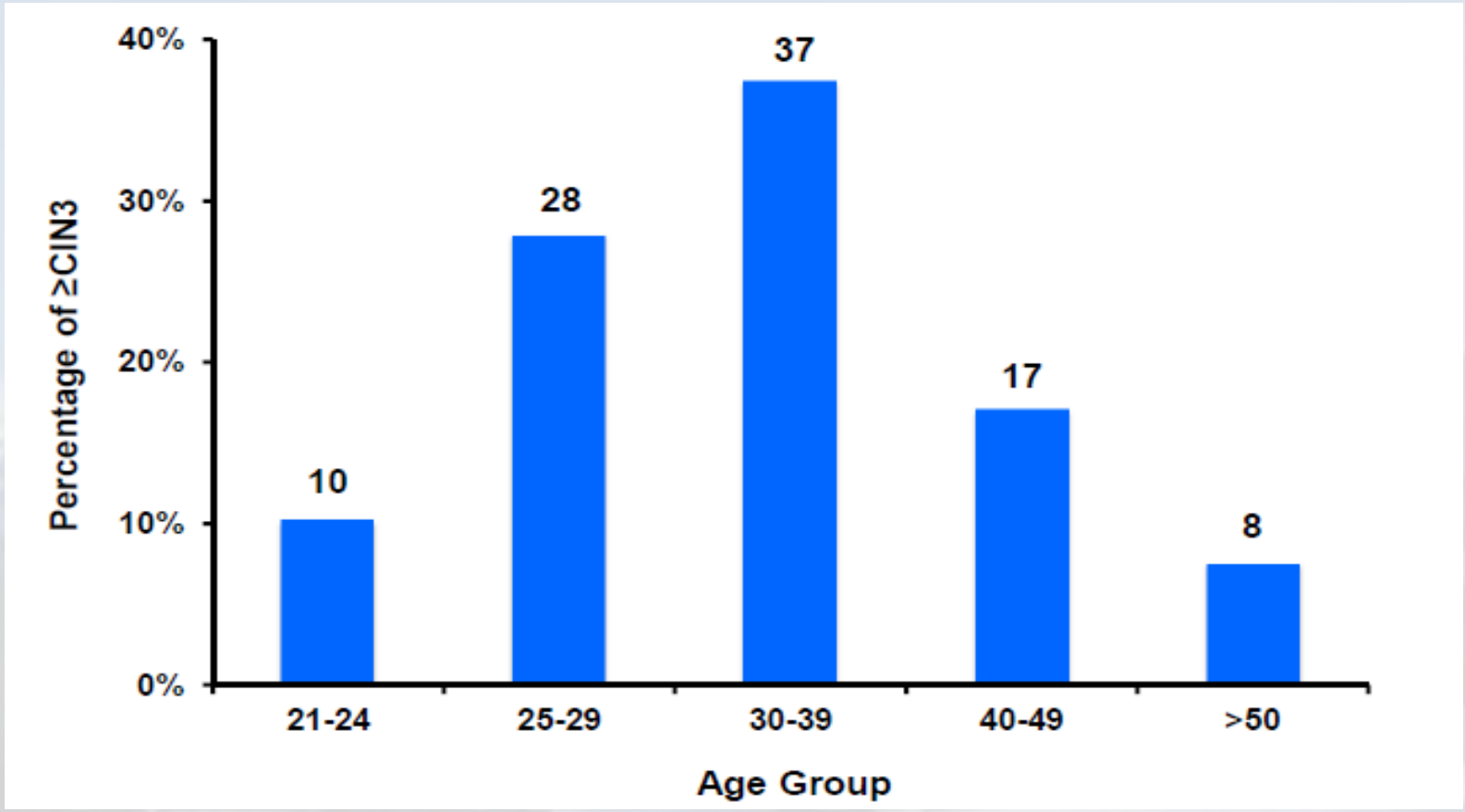
Reflex Cytology for All HPV Tests

- If reflex cytology not available Colposcopy recommended for + 16 or 18
- 16 and 18 pose greatest risk of CIN III so additional procedures recommended (Colposcopy with bx for NILM and Low-Grade Cytology and + 16 or 18 and Tx for HSIL cytology which is + HPV 16) Action threshold exceeds 60% for CIN III therefore expedited Tx recommended
- If reflex cytology not available from HPV sample then collecting cytology at colposcopy recommended. If HSIL still consider Excision even if Bx not HSIL

When start screening?



Rate of CIN III or Greater by Age in ATHENA



Percentages shown are for hrHPV+ women with ≥CIN3, N=252
Huh W, et al. 27th International Papillomavirus Conference, Berlin, Germany, September 17–22, 2011, OP-229.

Wright et al. *Am J Obst Gynecol*, 2011.

What next? *If Hx any indication 1^0 HPV aint the last stop*

- Dual Stain p16/Ki-67
  - Indicator of cell dysregulation
  - Improved sensitivity and reproducibility compared with cytology
  - Improved specificity combined with HPV typing vs. CoTesting
  - Very high NPV
  - Automated, could lead to completely molecular pap
- Extended Genotyping
  - e.g. 16, 31, 18, 33/58, 52, 45, 51 (Roche) 16, 18, 45, 31/33/52/58 (Abbott)
  - Predicts HSIL lesions with good sensitivity and specificity
  - Persistent and multiple HPV infection increases risk for dysplasia and progression
- DNA Methylation
  - Biomarker for clinically relevant HPV infection
  - Methylation accumulation can predict risk for progression to HG disease
  - >sensitivity cytology, < CoTest, but > specificity than both. Needs validation

Einstein et al. ObGyn.142,5 Nov 2023

What next?

- Self-Sampling
  - Gaining popularity in Europe and Australia
  - Similar performance to clinician obtained specimen
  - Reduce barriers to screening
  - NCI SHIP Trial across US representing racial, socioeconomic & ethnic diversity

- What about vaccinated populations?
  - No current recs
  - Evidence of decreased HPV, dysplasia and cancer
  - Test performance changes significantly with decreasing prevalence
  - PPV of cytology declines significantly

Self-collection

- Not yet FDA approved in US
- Multiple effectiveness studies and patient acceptability studies have shown that self-collection is effective, is cost-effective and is acceptable to women, especially among under-screened populations
  - Sensitivity comparable to clinician-obtained samples with PCR-based HPV tests.
  - A positive test requires a physician collected specimen for triage

Arbyn M, et al. Detecting cervical precancer and reaching underscreened women by using HPV testing on self-samples: Updated meta-analyses. *BMJ*. 2018;363:k4823

Bottom line

- Primary HPV screening works comparably to CoTesting
- Less complicated
- Potentially fewer exams and tests
- Potential to increase access and improve patient participation- Self collection.
- Can be cost efficient
- Need transition and preparation before widely available
- Any screen is better than no screen
- If you don’t like (like) the weather……. Just wait a minute


Thank you
Safe travels
&
Looking forward to the 50th!
See you then